Approved by the Regents
May 18, 2023

PROMOTION RECOMMENDATION
THE UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY

Raymond C. Trievel, Ph.D., associate professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School, is recommended for promotion to professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School.

Academic Degrees:

Ph.D.	2000	University of Pennsylvania
B.S.	1995	University of Delaware

Professional Record:

2015 - 2020	Associate Professor of Biophysics, University of Michigan
2009 - present	Associate Professor of Biological Chemistry, with tenure, University of Michigan
2003 - 2009	Assistant Professor of Biological Chemistry, University of Michigan

Summary of Evaluation:

Teaching: Dr. Trievel contributes significantly to teaching in the classroom and research laboratory, teaching both graduate and undergraduate-level courses. From 2010 – 2018 Dr. Trievel served as the course director and instructor for Biological Chemistry 415/515, an introductory biochemistry course that typically had around 200 students enrolled. Dr. Trievel has been teaching Biological Chemistry 452 for the past two years, which is the second semester of the advanced Biochemistry for majors. This class generally has around 70 students per year. At the graduate level, Dr. Trievel has taught Eukaryotic Gene Transcription (Biolchem 650), a course that he helped to develop. Comments provided by students on evaluations for this course focused on his commitment to excellence in teaching. In the laboratory, Dr. Trievel advances our educational mission by training a large number of scholars including Ph.D. students, master's degree students, post-doctoral students, and undergraduate students. He has served on an outstanding 52 thesis committees.

Research: Dr. Trievel is a respected and widely recognized expert in the structural enzymology of protein methyltransferases and other epigenetic histone-modifying enzymes that play critical roles in the regulation of gene expression. His lab has determined numerous structures of these enzymes and their ligands, and he has developed new assays for measuring the activity of methyltransferases and demethylases that have resulted in four granted patents and commercialized products. A highly recognized contribution of Dr. Trievel is the molecular determinants of product specificity in the broad family of SET domain protein methyltransferases, which can vary between mono-, di-, and tri-methylation. These enzymes perform diverse biological functions and are pursued as drug targets in multiple diseases. Dr. Trievel has published highly cited primary articles as well as authoritative reviews on the topic.

Dr. Trievel is also widely credited for recognizing a key role for CH---O hydrogen bonds in the active sites of methyltransferases, and these models have gained a high degree of acceptance in the field. His work points to the important role of tetrel bonding between the methyl group of the substrate S-adenosyl methionine and the nucleophile across a wide range of methyltransferases that work on proteins, nucleic acids, and small molecules. His work advances basic understandings of enzyme structure/function and has important implications for inhibitor development in methyltransferases as well as other medically important enzymes.

Dr. Trievel has shown strong productivity throughout his career, publishing 67 peer-reviewed publications in high-quality journals in his field, including the *Journal of the American Chemical Society*, *Journal of Biological Chemistry*, and *ACS Chemical Biology*. Dr. Trievel's research has been well funded by the National Institutes of Health (NIH) and the National Science Foundation (NSF). Dr. Trievel is a valued collaborator and currently serves as a co-investigator on an NIH R21 award with Dr. Melanie Ohi.

Recent and Significant Publications:

Abshire ET, Chasseur J, Bohn JA, Del Rizzo PA, Freddolino PL, Goldstrohm AC, Trievel RC*, "The structure of human Nocturnin reveals a conserved ribonuclease domain that represses target transcript translation and abundance in cells," *Nucleic Acids Res* 46(12): 6257-6270, 2018. PM29860338/PMC6158716

Fick RJ[#], Kroner GM[#], Nepal B, Magnani R, Horowitz S, Houtz RL, Scheiner S, Trievel RC*, "Sulfur-Oxygen Chalcogen Bonding Mediates AdoMet Recognition in the Lysine Methyltransferase SET7/9," *ACS Chemical Biology* 11(3): 748-754, 2016. PM26713889

Horowitz S, Dirk LM, Yesselman JD, Nimtz JS, Adhikari U, Mehl RA, Scheiner S, Houtz RL, Al-Hashimi HM, Trievel RC*, "Conservation and functional importance of carbon-oxygen hydrogen bonding in AdoMet-dependent methyltransferases," *J. Am. Chem. Soc.* 135(41): 15536-15548, 2013. PM24093804

Krishnan S, Trievel RC*, "Structural and Functional Analysis of JMJD2D Reveals Molecular Basis for Site-Specific Demethylation among JMJD2 Demethylases," *Structure* 21(1): 98-108, 2013. PM23219879

Del Rizzo PA, Couture JF, Dirk LM, Strunk BS, Roiko MS, Brunzelle JS, Houtz RL, Trievel RC*, "SET7/9 catalytic mutants reveal the role of active site water molecules in lysine multiple methylation," *J. Biol. Chem*. 285(41): 31849-31858, 2010. PM20675860/PMC2951256

Service: Dr. Trievel has been very involved in service. Within the department, he has served on many committees, including the communications committee, the seminar committee (that he chaired from 2015-2022), the graduate student admissions committee, the advisory committee, the safety committee, and the faculty search committee. He has also served on multiple committees for the Cellular and Molecular Biology program (CMB) and Biophysics. In addition to the service at the university, Dr. Trievel has been active on the national Life Science Collaborative Access Team (LS CAT) board and co-organized the American Society for Biochemistry and Molecular Biology (ASBMB) symposium on Transcriptional Regulation for several meetings (2010,2012, 2014, 2016).

External Reviewers:

Reviewer A: "Dr. Trievel's research is of the highest quality and addresses fundamental aspects of the chemistry of the methyltransferase reaction within these enzymes. In particular, I point out his discovery of the prominence and importance of carbon-oxygen hydrogen bonds in SAM binding to methyltransferases, and the roles of other less well recognized chemical interactions such as Sulfur-oxygen chalcogen bonding and methyl-Tetrel bonding. These are important aspects of how the cofactor binds to the enzyme and these new physico- chemical concepts will be important for drug discovery efforts against methyltransferases."

Reviewer B: "Dr. Trievel's laboratory has continued to produce outstanding papers that provide us with new insights in how methyltransferases recognize their substrates and catalyze methyl transfer reactions. He has also expanded his work to study the mechanisms of the demethylases that reverse the methyl modification of histones and other proteins. He is clearly the leader in this field and is the dominant player in our understanding of SET-domain methyltransferases. He has recently branched out to look at other enzyme classes, including those involved with homocitrate metabolism. He is clearly one of the best enzymologists of his generation of scientists and our field of methylation is lucky to have him!"

Reviewer C: "Ray has published over two dozen papers since becoming Associate Professor, most in top journals in biochemistry. He has received substantial grant support including a prestigious federal grant from the National Institutes of Health. This level of productivity and innovative research merit the stature of a full Professor at major research universities…Outside of his research accomplishments, it appears that Ray plays key educational roles and administrative functions at the University of Michigan and has continued to do substantial national service with regard to journal editorial activities and grant reviewing."

Reviewer D: "Dr. Trievel is heavily involved in teaching of advanced coursework. He has taught Biology and Chemistry of Enzymes, Advanced Biochemistry II, Biochemical Regulatory Mechanisms and Eukaryotic Gene Transcription (currently a course codirector). This teaching load of advanced courses speaks of his qualities as an instructor, as well as his willingness to contribute to training of the next generation of scientists."

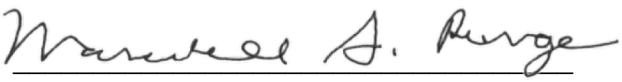
Reviewer E: "Dr. Trievel has clearly demonstrated excellence in all areas necessary for this promotion – research, teaching, and service activity…Remarkably, his research is currently supported by several active grants, such as NIH R01, NIH R21 and NSF CHE. Raymond has published a number of pioneering studies in the pivotal areas of biology, including his top-notch studies…Overall, he has published 66 research papers and 3 book chapters. Dr. Trievel has presented his research at a number of national and international scientific conferences and Universities."

Reviewer F: "In addition to his work on lysine methyltransferases, Dr. Trievel has made seminal discoveries into the structure and function of the Jumonji domain containing lysine demethylases. Dr. Trievel published [sic] one of the first structures of this enzyme class. Similar studies have been extended to other members of this family including JMJD5. One of the things that impress [sic] me most about Dr. Trievel's work is that he is not only a world class crystallographer by an adept enzymologist who has developed several innovative approaches and assays to study enzymes involved in chromatin biology."

Reviewer G: "Dr. Trievel's accomplishments are of [a] higher caliber than a majority of colleagues in the discipline who have been promoted to full professor in other leading research universities. He has excelled himself as a world expert and leader in the protein methylation and epigenetics field. His approach is innovative and mechanistic, and the results have significant impacts on histone modification, PTM biology, and fundamentals of biochemistry. The study of epigenetics-regulating PTMs is one of the frontiers of life science research. Dr. Trievel was able to establish his eminence and leadership in this exciting research area."

Reviewer H: "Many of his trainees not only do great work but also have developed into productive independent academic leaders themselves. As a former trainee in the Biological Chemistry program at Michigan, I am grateful to my mentor Rowena Matthews and others like Ray…I also want to highlight Ray as a collaborative leader of the community."

Summary of Recommendations:
Dr. Trievel has distinguished himself as an exceptional researcher that is nationally and internationally recognized as a leader in the field of S-adenosylmethionine-dependent methyltransferases. He continues to be highly productive with excellence in teaching, mentorship, as well as service. I am pleased to recommend Raymond C. Trievel, Ph.D. for promotion to professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School.



Marschall S. Runge, M.D., Ph.D.
Executive Vice President for Medical Affairs
Dean, Medical School

May 2023